Citalopram in newborns: A case report.

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INTRODUCTION

Neonatal withdrawal syndrome is usually attributed to the exposition of the foetus to drugs of abuse in utero. In the period 2001 – 2006 we were confronted with several cases with withdrawal symptoms caused by citalopram taken by the mother during the pregnancy for psychiatric indication. First meconium and urine were sent for drug of abuse screening. Only a good cooperation with the neonatologist helped to find out that citalopram was given to the mother after exclusion of other drugs. Targeted analysis on citalopram was then performed. Published studies evaluating the safety of selective serotonin reuptake inhibitors (SSRIs) during pregnancy show that abstinence syndrom appears in about 30 % of neonates exposed to SSRIs in utero, especially in the last trimester of pregnancy (1-6). As this information is not sufficiently known yet, the aim of this presentation is to draw attention of toxicologists to the risk of SSRIs (eg.citalopram) for newborns and to the possibility of analytical confirmation of citalopram exposure in utero.

EXPERIMENTAL

Analytical methods

a) Meconium : 1g of meconium was homogenized in methanol.Homogenate was sonicated and frozen. The upper layer was discarded and the sample was centrifuged. Methanol was evaporated to dryness, residue taken in 0.5ml of methanol and 3 ml of phosphate buffer pH 8 and screened by EMIT for drugs of abuse.
Isolation was then done by SPE on CHEM ELUT columns with dichloromethane – 2-propanol 90 : 10.
Two dimensional high performance thin layer chromatography (HPTLC) on HPTLC Kieselgel 60 glass plates 10 x10 cm (Merck) was used for analysis. Mobile phase:
1st direction: ethylacetate – methanol- ammonia 8.5 : 1.0 : 0.5, 2nd direction: methanol – amonia 9.9 : 0.1. Dragendorff reagent was used for visualization. Limit of detection for citalopram was 0.5µg/g. The analytical procedure is described in (7,8).

b) Urine: isolation of sample volumes 8 ml and higher was done by extraction with diethylether from alkaline milieu pH 8. SPE on CHEM ELUT columns was used for smaller sample amounts .
TLC according to the laboratory protocol was used for analysis. LOD for citalopram in urine was 0.05 mg/l.
c) Blood: a 1ml volume of serum was mixed with 50 µl of internal standard imipramine (resulting concentration 20 ng/ml) and 0.5 ml 1 mol/l sodium hydroxide and extracted by

4ml of hexane with 1% of 2- propanol. 3ml of the upper layer were reextracted with 250 µl 0.1 mol/l hydrochloric acid, frozen out and 150 µl of water layer were injected on the column. Quantitative analysis was performed by HPLC on Waters chromatographic system with photodiodearray detector, operated in isocratic mode with guard (30 mm x 3 mm I.D.)and analytical reversed phase (150 mm x 3 mm I.D.)columns packed with octadecylsilica Separon SGX C_{18}, mobile phase acetonitrile –phosphate buffer 1: 1 v/v(1l of 0.01 mol/l phosphate with 1.2 ml nonylamine, adjusted to pH 3 with phosphoric acid)(9). LOD of citalopram was 2 ng/l, LOQ 10 ng/ml. Calibration curve was linear in the range 10 – 200 ng/ml.
The same method was used for semiquantitative estimation of citalopram amount in urine. It was not validated for urine.

CASE REPORTS

We encountered altogether 7 cases of newborns exposed to citalopram in utero.

Case 1 appeared in 2001 and is presented in more detail as there are most data available .
Symptoms of withdrawal in the baby – increased irritability, restlessness, shivering, followed by depression- appeared 30 hours after delivery.
Screening for drugs of abuse in meconium and urine was negative. Trying to find the reason of baby`s health state the physician found out that the mother had been taking citalopram during the whole pregnancy from psychiatric reasons.
Subsequently analysis targeted on citalopram was required and performed. Citalopram was detected in urine.
As the withdrawal symptoms persisted urine and blood of the baby and blood of the mother were sent for analysis 4th day after delivery.
Analytical results are presented in Table 1.

Table 1: Case 1-analytical results

	Specimen collection	
	2nd day	**4th day**
meconium	negative	-
urine	citalopram	citalopram
serum(baby)	-	citalopram - 5 ng/ml
Serum (mother)	-	citalopram - 22 ng/ml

The child suffered from neurological problems in his toddler age which was considered to be a consequence of citalopram poisoning.
The second child of this mother born 2.5 years later (case 4, Tab.2), displayed the same symptoms as his older sibling, only milder. This time only urine collected for 12 hours after delivery was sent for analysis .
Result : urine- citalopram and metabolite; concentration of citalopram 2184 ng/ml.
Overview of data available for all analyzed cases is presented in Table 2.
Symptoms appearing in single cases are presented in Table 3.

Table 2: Data available for all analyzed cases

Case /year	Citalopram dose /day	Specimen collect. after	Identification		Concentration *(ng/ml)*	
			meconium	urine	blood	urine
1/2001	20 mg	1st 30 hours	neg.	citalopram	NA	-
		2nd 4 days	NA	citalopram	5 *	-
2/2001	10 mg +1	24 hours	THC	trace of citalopram	NA	-
3/2003	unknown	24 hours	neg.	not delivered	NA	-
4/2003	20 mg	for 12 hours after birth	NA	citalopram +norcit.	NA	2184
5/2005	unknown	24 hours	neg.	citalopram	NA	-
6/2006	unknown +2	18 days	NA	neg.	NA	-
7/2006	20 mg +3	2 days mec.	neg.	-	NA	799 norcit. 72
		3 days urine, blood	-	citalopram +norcit.	neg.	

* mother 22 ng/ml

\+ = further probable or known therapy and circumstances

\+ [1] + ½ tbl chlorpromazine; mother admitted marihuana smoking during pregnancy
\+[2] + chlorpromazine , zopiclone. oxazepame; premature delivery
\+[3] + 200 mg quetiapine
NA - not available

norcit. - norcitalopram (desmethylcitalopram)

DISCUSSION

Citalopram was always detected only in urine, not in meconium. Analytical procedure was tested on meconium spiked with citalopram in concentration range 2.0 – 0.1µg/g . Detection limit was 0.5 µg/g. The reason for negative findings in meconium might be the isolation step, because of heterogenity of meconium and high lipid content in the sample. We had no opportunity to test various isolation procedures with original specimens, because the amount remaining after drug of abuse screening was always too small. We also did not find any references about analysis of citalopram in meconium.
Citalopram concentration found in the case 1 in serum of both infant and mother were in therapeutical range, in case 7 citalopram was undetectable. This corresponds with the results of Heikkinen et al.(10) who measured the concentration of citalopram in serum after delivery and during breast feeding.

The data about other medicaments than citalopram taken by the mother (Table 2) in cases 2,6, are known only from mothers, not from any official documentation. Therefore it was not possible to estimate the dose really taken. Neverthless none of these drugs was detected in the urine of the babys`. Moreover, the case 6 was complicated by an infection that appeared within 4 days after birth and the urine sample delivered to the laboratory was taken on the 18th day.
The data in the case 7 are known from medical documentation. Mother was taking escitalopram 20 mg/day and quetiapine 200 mg/day. Quetiapine was neither detected in meconium nor in urine.
There are only a few studies about the influence of citalopram and some other SSRIs on the neonates, sometimes with contradictory conclusions. Neverthless, most of them state clearly that withdrawal symptoms occured within few days after birth and lasted up to one month at least at 30 % of neonates.

Table 3: Clinical symptoms

Case	Symptoms
1/2001	increased irritability, restlessness, shivering; later persisting depression
2/2001	birthweight 2.275g, light irritability, without abstinence syndrome; mother smoked marihuana several times per month during pregnancy
3/2003	Finnegan score 16 points during 18 hours
4/2003	same as in the case 1, only milder
5/2005	increased brain irritability, striking restlessness, trembling of limbs, apnoic pause, transitory disorder of blood circulation; improved after about 30 hours but tendency to cramps persisted
6/2006	premature delivery, hypotrophic neonate; very depressed, eating difficulties, vomitting, watery stool; symptoms persisted over 14 days
7/2006	agitation, shivering, sleeping problems, febrility; improved after 48 hours, 5th day agitation and increased irritability again

CONCLUSIONS

Withdrawal symptoms appearing in neonates needn`t be necessarily caused only by drugs of abuse but also by other therapeutic drugs as SSRIs .
Urine is suitable biological specimen for citalopram detection. Analysis of meconium on citalopram was not successful.
Citalopram blood levels in neonates were very low or even undetectable.

The risk of citalopram (or other similar psychopharmacological agents) for neonates is not widely known yet, therefore more information about such cases are needed.

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